



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re Patent Application of

UKAI et al

Atty. Ref.: 423-54

Serial No. 09/462,633

Group: 1615

Filed: January 27, 2000

Examiner: Pulliam

For: **STABILIZED COMPOSITION COMPRISING A BENZIMIDAZOLE TYPE COMPOUND**

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Assistant Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, Yoshiteru Kato, declare as follows:

I am a citizen of Japan residing at the address given in my Rule 63 Declaration.

Address: Kisogawa-chou, Haguri-gun, Aichi, Japan 493-0001

I graduated from Toyama Medical and Pharmaceutical University, Department of Pharmacy, in 1988, where I studied biopharmaceutics, age-dependent changes in drug tissue distribution and was awarded the degree of PhD in pharmacy in 1988. Since 1988 I have been employed by Eisai Co., Ltd., the assignee of the subject application, and remain there now where I have been studying the formulation of solid dosage forms in Eisai's Formulation Research Laboratories.

I am familiar with the Official Action of November 5, 2001 and the published documents cite in it, particularly the WO 97/25066 to Depui et al, U.S. patent 6,030,988 to Gilis et al and U.S. patent 5,708,017 to Dave et al.

In our application as above-identified, we describe stabilization of sodium rabeprazole by the addition of sodium hydroxide and found that sodium hydroxide is a

suitable stabilizer for sodium rabeprazole compared with other alkaline agents. The purpose of this study was to compare the use of sodium hydroxide to stabilize the benzimidazole-type compound, sodium rabeprazole, compared with other alkaline agents, i.e. sodium citrate, aluminum hydroxide and others.

The following experiments were conducted by me or under my supervision and control:

Sample tablets were prepared as follows: Sodium rabeprazole was combined with a selected alkaline agent and excipients, subjected to wet granulation, dried and then compressed into a tablet. Amounts of individual components for each formulation in this study are shown in Table 1.

When sodium hydroxide was used as an alkaline agent, the typical preparation method was as follows: 1.5g of hydroxypropyl cellulose and 62g or 61.5g of mannitol were added to and mixed with 10g of sodium rabeprazole, and then 0.5g or 1.0g of sodium hydroxide dissolved in 5g or 7g of ethanol was gradually added to the mixture under stirring to make granules which were dried in a tray dryer and milled gently using an agate mortar, respectively. When 20g of sodium hydroxide were combined, they were mixed with 1.5g of hydroxypropyl cellulose, 42.5g of mannitol and 10g of sodium rabeprazole and then granulated as above. After weighing the milled granules, an adequate amount of magnesium stearate to assist in tableting was added proportionally according to the formulation in Table 1 and tabletted to give 7.5mm diameter tablets each weighing 150 mg containing 20 mg of sodium rabeprazole.

When alkaline agents other than sodium hydroxide were used, the typical preparation method was as follows. These alkaline agents were sodium citrate as a sodium cation, sodium phosphate as a sodium cation, aluminum hydroxide as a hydroxide anion, calcium hydroxide as a hydroxide anion or magnesium hydroxide as a hydroxide anion. 0.5g of sodium phosphate, 1.5g of hydroxypropyl cellulose and 62g of mannitol were added to and mixed with 10g of sodium rabeprazole, and then 5g of ethanol were gradually added to the mixture under stirring to make granules which were dried in a tray dryer and milled gently using an agate mortar. After weighing the milled granules, an

adequate amount of magnesium stearate as a tableting aid was added proportionally according to the formulation in Table 1 and tabletted to give 7.5 mm diameter tablets each weighing 150 mg containing 20 mg of sodium rabeprazole.

Each tablet prepared as above was placed in a glass bottle and stored in a cold place, at 60 °C or at 40 °C-75% relative humidity, with the bottle opened, for 1 week then the color difference(ΔE), content and amounts of product degradation were measured. Each formulation stored was evaluated based on the color difference (ΔE), measured by a color-difference meter (SZ-Σ90, Nippon Denshoku Kogyo), as an index of the change in the color (coordinate (L), saturation (b) and hue (a)) observed when stored at 60 °C or at 40 °C-75% relative humidity when compared with the control which was stored in the same cold place.

The contents and amounts of product degradation of sodium rabeprazole were determined by high performance liquid chromatography and the contents were shown as the relative percentages as the initials.

The results of these studies were analyzed by various criteria.

Preparation Suitability: When 20 parts by weight of sodium hydroxide (Experiment 4) were combined with 10 parts by weight of sodium rabeprazole, the milled granule was very hygroscopic and it was too difficult to tablet the granules. For this reason there are no data of Experiment 4 in Tables 2, 3 or 4.

Color Difference: The values of the color difference (ΔE) in each experiment are shown in Table 2. A larger color difference (ΔE) reflects a larger color change of a sample stored under stressed conditions compared with a control stored in the cold place.

The color differences (ΔE) of sodium hydroxide-supplemented samples were the smallest in all experiments under 60 °C and 40 °C-75% relative humidity conditions when 0.5 part of weight of some alkaline agents was combined with 10 parts by weight of sodium rabeprazole. Sodium phosphate and calcium hydroxide were also effective to reduce color difference (ΔE) under 60 °C condition but more than 20 parts by weight of the alkaline agents were necessary for 10 parts by weight of sodium rabeprazole to inhibit

color change. On the contrary, sodium hydroxide had an effectiveness in inhibiting the color change of sodium rabeprazole under stressed conditions at a much smaller amount, 0.5 to 1 part by weight for 10 parts by weight of sodium rabeprazole. Furthermore, when crospovidone was added the color change was inhibited especially under 40 °C-75% relative humidity condition.

Content and Amount of Product Degradation: The content and amount of product degradation of sodium rabeprazole in each experiment under stressed conditions are shown in Table 3 (content) and 4 (degradation product amount), respectively.

As shown in Tables 3 and 4, sodium hydroxide (Experiment 2, 3) stabilized sodium rabeprazole under all stored conditions more than sodium citrate (Experiment 5, 6), aluminum hydroxide (Experiment 9, 10) or magnesium hydroxide (Experiment 13, 14) did. Sodium citrate, aluminum hydroxide and magnesium hydroxide had almost no effect on the stability of sodium rabeprazole independent of the amount added when compared with control (Experiment 1). Calcium hydroxide did not stabilize sodium rabeprazole when 0.5 part by weight of calcium hydroxide was combined with 10 parts by weight of sodium rabeprazole and more than 20 parts by weight of calcium hydroxide were necessary for 10 parts by weight of sodium rabeprazole to stabilize sodium rabeprazole. When 0.5 or 20 parts by weight of sodium phosphate were combined with 10 parts by weight of sodium rabeprazole, sodium phosphate stabilized sodium rabeprazole compared with control, but it did less than sodium hydroxide did. Sodium hydroxide stabilized sodium rabeprazole even when used in a small part (from 0.5 to 1) by weight of sodium hydroxide was combined with 10 parts by weight of sodium rabeprazole.

From these data and based upon my own prior experience I concluded sodium hydroxide is a highly effective and efficient stabilizing agent for sodium rabeprazole compared with other alkaline agents.

I hereby declare that all statements made herein of any own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the

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like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 30. Oct. 2002 Yoshiteru Kato
Yoshiteru Kato